Journal Name

COMMUNICATION

Iron catalyzed diastereoselective hydrogenation of chiral imines

D. Brenna,[a] S. Rossi, [a] F. Cozzi[a] and M. Benaglia[a*]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

ABSTRACT: Cyclopentadienone-based iron complexes were used for the first time to succesfully catalyze the diastereoselective hydrogenation of enantiopure imines. Chiral amines, including valuable biologically active products, were obtained often as enantiomerically pure compounds. Computational studies helped to elucidate the chemical and stereochemical aspects of the iron-catalyzed reaction.

Strong efforts are currently devoted to the development of new catalysts based on non-noble transition metals, like iron and cobalt. In this context, an increasing number of transformations promoted by iron catalysts have recently been reported.[1] Being iron a cheap and abundant element of low toxicity,[2] iron-based catalysts are excellent candidates for application in the fine chemical industry.

While the iron-promoted reduction of carbonyl groups[3] has been extensively studied,[4] the corresponding hydrogenation of C=N double bonds has been much less explored and only very limited results have been reported. In 2011 Beller[5] described different combinations of iron cyclopentadienone-based catalysts[6] and chiral phosphoric acids as efficient catalytic systems to enantioselectively reduce imines. Later, Morris[7] described for the very efficient reductions of ketones a new chiral iron complex, which was also used to reduce a very limited number of imines. Finally, in 2015 Renaud[8] developed an achiral class of iron catalysts with enhanced reactivity in imine reduction compared to previous complexes.[9]

Noteworthy, only Beller's and Morris' works dealt with the stereoselective reduction of C=N bonds,[5,7] to afford chiral amines, despite the fact that this class of compounds are of enormous importance, for instance in the pharma industry.[10] With this work, we decided to explore the iron-catalyzed reduction of imines featuring a removable chiral auxiliary, as a simple methodology to obtain enantiopure amines

We initially focused our attention on the reduction of *N*-(1-(*R*)-phenylethyl)-imines, featuring an inexpensive chiral residue, readily available in both enantiomeric forms and generally obtained in the configurationally stable *E* configuration. Three different catalytic systems were selected for preliminary studies, the Knölker complex **A**,[11] the iron complex proposed by Renaud, **B**[8] and a modified Knölker-like system, **C**.[12] These precatalysts required *in situ* activation by addition of trimethylamine *N*-oxide (TMANO), under hydrogen pressure.

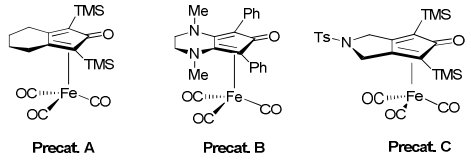
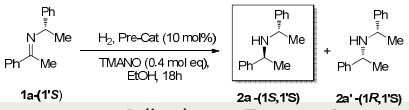


Figure 1: Iron pre-catalysts **A-C**.

The catalysts were tested in the reduction of *N*-(1-(*S*)-phenylethyl)-ethan-1-(phenyl)-1-imine **1a** (Table 1).

Table 1: Preliminary studies on iron-catalyzed imine reduction.



Entry	Pre-Cat.	P (bar) [a]	T (°C)	Conv. (%)[b]	Yield	*dr* [b]
1	**A**	30	70	41		97:3
2	**A**	30	100	<5		60:40
3	**A**	80	25	-		-
4	**B**	30	40	26		93:7
5	**B**	30	50	47	41	92:8
6	**B**	30	70	98	96	93:7
7	**B**	80	25	-		-
8	**C**	30	70	34	30	98:2
9	**C**	30	100	< 5		60:40
10	**C**	80	25	-		-
11	$Fe_2(CO)_9$	EtOH	70	14		60:40
12[c]	**A**	30	50	16		95:5
13[d]	**A**	30	50	19		92:8
14[c]	**A**	30	70	30		92:8
15[c]	**B**	30	50	-		-

[a] reactions run on 0.2 mmol of imines in 2 mL of degassed ethanol. [b] conversion and *d.r.* evaluated by NMR on the crude reaction mixture after

removal of the iron particles by filtration. [c] 1 mol eq of salicylic acid was added. [d] 0.5 mol eq of salicylic acid was added.

Working at 70°C, catalyst **A** showed a modest activity, leading to the desired amine **2** in high stereoselectivity (d.r. 93:7) but in a modest 41% yield (entry 1).The more electron rich pre-catalyst **B** (entry 6) promoted the reduction with excellent yield (up to 96%), and diastereoisomeric ratio (up to 93:7). With complex **C**, the product was isolated with almost complete stereoselectivity (d.r. 98:2), but in lower yields.‡

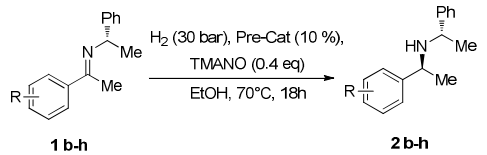
At low temperature and high hydrogen pressure (entries 3, 7 and 10) the reduction did not proceed at all, and the starting material was recovered unreacted. At 100°C low yields and modest stereoselectivities were observed, independently from the employed catalyst (entries 2 and 9). Under these harsh conditions, the release of iron from the cyclopentadienone ligand with concomitant generation of iron particles was observed. In the attempt to assess the catalytic activity of those particles, the reaction was run at 100°C in the presence of catalytic amounts of $Fe_2(CO)_9$, a notoriously thermally instable source of iron (entry 11). With this catalyst, conversion and stereoselectivity analogous to those recorded in the high temperature experiments were observed, thus suggesting that at higher temperature the reaction was promoted only by species generated upon catalyst decomposition.

In the attempt to accelerate the reaction by imine protonation to generate the iminium ion, the addition of an acid to the reaction mixture was studied. However, the reduction promoted by complex **A** in the presence of salicylic acid afforded the product in much lower yield and slightly but significantly lower stereoselectivity than in the reaction without acid (entries 12-14 vs 1).# Using complex **B** no conversion was observed, probably due to deactivation of the catalyst by ligand protonation.

With the optimized conditions for each catalyst in our hands (Table 1), we explored the scope of the reaction. Imines with different substituents on the C-bound aromatic ring were reduced at 70°C in ethanol under 30 bar of hydrogen (Table 2). Catalyst **B** constantly proved to be the most active, affording the expected amines in modest to good yields and high stereoselectivity.

With electron-donating group-substituted aryl residues (electron rich imines), the products were isolated in up to 65 % yield (entry 1 and 7), while, using electron poor imines, lower yields were observed, in accordance with a recently reported work related to the iron-catalyzed direct amination of benzyl alcohols (see also discussion below).[13]

Table 2: Iron-catalyzed reduction of chiral imines: reaction scope



Entry[a]	R	Cat.	Prod n°	Conv. (%) [b]	Yield (%)	*dr*[b]
1	4-OMe	**B**	**2b**	65	63	92:8
2	3-OBn	**B**	**2c**	55	55	>98:2 [c]
3	3-OMe	**B**	**2d**	49	45	97:3
3	4-Cl	**A**	**2e**	20		98:2
4	4-Cl	**B**	**2e**	53	47	>98:2
5	4-Cl	**C**	**2e**	10		98:2
6	4-Me	**A**	**2f**	20		95:5
7	4-Me	**B**	**2f**	67	65	92:8
8	4-Me	**C**	**2f**	40		87:13
9	4-CF_3	**B**	**2g**	5		67:33
10	4-NO_2	**B**	**2h**	30	27	72:28
11	4-NO_2	**C**	**2h**	10		65:35

[a] reactions were performed on 0.2 mmol of imines in 2 mL of degassed ethanol; [b] conversion and *d.r.* were evaluated by NMR on crude mixture after removal of the iron particles; [c] NMR analysis before column purification showed a 95/5 d.r..

Having developed an efficient method to stereocontrol the imine C=N bond reduction, we turned our attention to the removal of the chiral auxiliary, an essential step to access chiral primary amines. With the aim to avoid also in this step the use of precious transition metals, commercially available (*R*)-1-(4-methoxyphenyl)-ethylamine was used as a chiral auxilliary (eq. A, Figure 2), that would be possible to remove under mild oxidative degradation.[14] We were please to find that good yield and stereoselectivity were observed in the reduction of imine **1i**. The removal was efficiently performed on the *N*-acetylated derivative, by reaction with DDQ that afforded the deprotected derivative in 67% overall yield (for experimental details, see the Supporting Information).

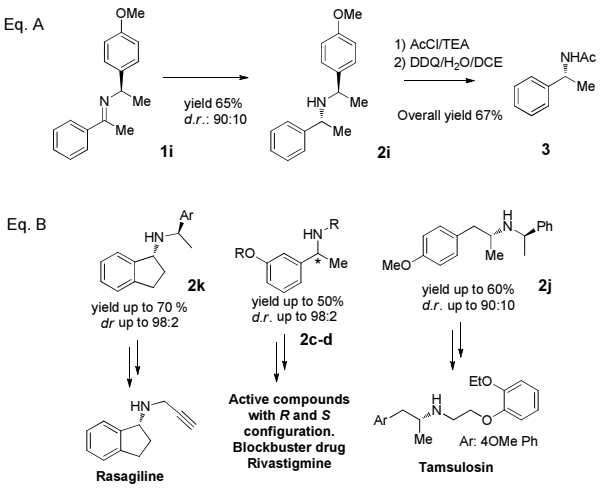


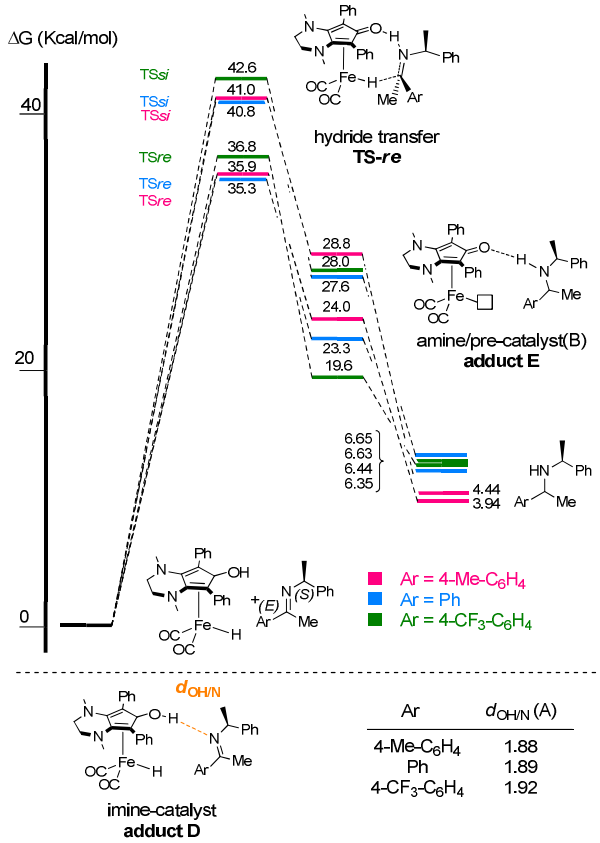
Figure 2: Synthesis of pharmaceutically active compounds.

Even better results were obtained in the synthesis of advanced precursors of pharmaceutically relevant ingredients (eq. B,

Figure 2).[15] Amine **2k**, a direct precursor of Rasagiline, used in the treatment of Parkinson disease,[16] was isolated in 70% yield as enantiomerically pure product. Amines **2c** and **2d,** 1-(*meta* alkoxyphenyl)-ethylamines, obtained in >97/3 d.r. (see Table 1), are direct precursors of several APIs, like Rivastgmine, and calcimimetic (*R*)-NPS 568,[17] while chiral amine **2j**, advanced intermediate of Tamsulosin,[18] was isolated with 60 % yield and 90:10 diasteroisomeric ratio.

In order to better elucidate the reaction mechanism and to rationalize the steric course of our reactions, computational studies were performed. The reductions of (*E*) *N*-(1-(*S*)-phenyl)ethyl imines derived from differently substituted acetophenones promoted by precatalyst **B** were studied, and the lowest energy transition states (TSs) leading to the formation of (1R,1'S) and (1S,1'S) amines, respectively, were located. After preliminary Monte Carlo conformational analysis, the lowest energy structures leading to the formation of (1R,1'S) and (1S,1'S) diastereoisomers, were optimized to the relative TSs by DFT calculations performed with GAUSSIAN 09 program, using the hybrid B3LYP functional for all atoms except for iron.¥

A superimposed cross section of the reaction profiles for the reduction of (*E*)-imines derived from acetophenone (**1a**), 4'-methyl acetophenone (**1f**) and 4'-(trifluoromethyl) acetophenone (**1g**) is reported in Figure 3 (see supporting information for the complete energy profile and further data).



Ar	$d_{OH/N}$ (A)
4-Me-C_6H_4	1.88
Ph	1.89
4-CF_3-C_6H_4	1.92

Figure 3: Energy profile for the catalyzed reduction of imines (free energy values (B3LYP/6-31G(d,p) Fe(SDD) level), in kcal mol^{-1}). For a 3D representation of the structures see the SI.

Our calculation indicates that at the reaction outset, all the imines were coordinated by the hydrogenated form of **B** to give the corresponding adduct **D**. As expected, this substrate/catalyst coordination is energy demanding[8] and the hydrogen bond is significantly bent out of a linear alignment.

The hydrogenation of imines have been described to proceed according to two different pathways: a synchronous process, where both the hydrogen proton and the hydride are transferred simultaneously (as proposed by Renaud[8]); or a two steps process (formally the protonation of imine nitrogen atom followed by the transfer of the hydride) as reported by Berkessel for *N*-*t*-butyl substituted aromatic keto-imines.[19]

Analysis of the diastereoisomeric TS's involving the *Re* and *Si* faces (**TS*Re*** and **TS*Si***) revealed that the transfer of the hydride from the iron atom to the carbon atom happens when the proton transfer from the hydroxy group of hydrogenated catalyst **B** to the imine nitrogen has already almost completely occurred in a mechanism that we can define concerted but asynchronous (see the SI, Figure S6). Indeed, a clearly defined two-steps mechanism could be considered as an exception, as already remarked.[19] Finally, after the transfer of both hydrogen atoms to the imine, the resulting adduct **E** is formed and dissociates to afford the free amine and pre-catalyst **B**, which will re-enter the catalytic cycle once that it has taken up a new molecule of hydrogen.

Looking at the energy values in Figure 3, the TSs at lower energy are those responsible of the hydride transfer onto the *Re*-face of the (1S')-imines, and lead to the favored (1S,1'S)-isomers, in qualitative agreement with the experimental data. Moreover, electron-rich imines, that are reduced in higher yields, have indeed TSs of lower energy than those of electron poor counterparts (4-CH_3Ph~ Ph < 4-CF_3Ph). Although the calculations well rationalize the diastereoselectivity and the order of reactivity of the imines, the poor or inexistent reactivity of electron poor imines is not easily accounted for. A possible explanation could be that *N*-protonation to generate a more reactive iminium ion (see adduct **D**), is more facilitated with electron rich imines, due to their nitrogen higher basicity. The observation that the OH-N distance in adduct **D** for the CF_3-substituted imine is longer than in the Me-substituted substrate can tentatively lend support to this interpretation (Figure 3).

In conclusion, we have reported the first iron-catalyzed diastereoselective reduction of chiral imines; the method leads to the formation of chiral amines, often isolated as enantiomerically pure products. The synthesis of advanced intermediates of highly valuable APIs demonstrates the possibility to apply iron catalysis in the fine chemical industry.

D. B. thanks University of Milan for a PhD fellowship; S. R. thanks University of Milan for a postdoctoral fellowship.

Notes and references

‡ The reaction tested in other solvents, including toluene, anisole, glycols and water, did not work or gave very low yields.
# The use of other acidic additives did not lead to any appreciable different result.
¥ The SDD functional with default parameters was used for iron to account for the influence of occupied *d*-orbitals. The geometry of intermediate complexes and transition states was optimized in the gas phase without geometry constraints using the 6-31G(d,p) basis set for all atoms except for iron, which was described by the SDD basis set (for further details see SI).

1 For an extensive review on iron catalyzed reactions see: I. Bauer, H. Knölker, *Chem. Rev.,* 2015, **115,** 3170–3387.
2 For a recent review on metal toxicity see: K. S. Egorova, V. P Ananikov, *Angew. Chem. Int. Ed.,* 2016, **55**, 12150–12162.
3 For stereoselective reductions of ketones see: review, (a) L. C. Misal Castro, H. Li, J.-B. Sortais, C. Darcel, *Green Chem*., 2015, **17**, 2283–2303. For selected examples of enantioselective catalytic reductions of ketones, see: (b) A. Berkessel, S. Reichau, A. Von der Höh, N. Leconte, J. M. Neudörfl, *Organometallics*, 2011, **30**, 3880–3887; (c) D. E. Prokopchuk, J. F. Sonnenberg, N. Meyer, I. M. Zimmer-De Iuliis, A. J. Lough, R. H. Morris, *Organometallics*, 2012, **31**, 3056-3062; (d) A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.*, 2009, **131**, 1394; (e) N. Meyer, A. J. Lough, R. H. Morris, *Chem. Eur. J.*, 2009, **15**, 5605; (f) P. E. Sues, A. J. Lough, R. H. Morris, *Organometallics*, 2011, **30**, 4418; (g) P. O. Logaditis, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.*, 2011, **133**, 9662-9665; (h) A. Naik, T. Maji, O. Reiser, *Chem. Commun.*, 2010, **46**, 4475; (i) P. Gajewski, M. Renom-Carrasco, S. Vailati Facchini, L. Pignataro, L. Lefort, J. G. de Vries, R. Ferraccioli, A. Forni, U. Piarulli, C. Gennari, *Eur. J. Org. Chem.*, 2015, 1887–1893; (j) see ref. 7. (k)) For an account on chiral iron complexes, see R. H. Morris, *Acc. Chem. Res.,* 2015, **48**, 1494-1502. For a dual catalytic iron/lipase system, used in a DKR process, see: (l) O. El-Sepelgy, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed*., 2016, **55**, 13602 –13605.
4 For iron catalyzed hydrogenation reviews see: (a) B. A. F. Le Bailly, S. P. Thomas, *RSC Adv.*, 2011, **1**, 1435-1445; (b) R. H. Morris, *Chem. Soc. Rev.*, 2009, **38**, 2282-2291; (c) K. Junge, K. Schröder, M. Beller, *Chem. Commun.*, 2011, **47**, 4849-4859; (d) T. Zell, D. Milstein, *Acc. Chem. Res*., 2015, **48,** 1979-1994; (e) Y.-Y. Li, S.-L. Yu, W.-Y. Shen, J.-X. Gao, *Acc. Chem. Res.*, 2015, **48**, 2587-2598.; (f) for a recent contribution, see: U. Piarulli, S. Vailati Facchini, J.-M. Neudörfl, L. Pignataro, M. Cettolin, C. Gennari, A. Berkessel, *ChemCatChem*, 2017, DOI: 10.1002/cctc.201601591.
5 (a) S. Zhou, S. Fleischer, K. Junge, S. Das, D. Addis, M. Beller, *Angew. Chem. Int. Ed.*, 2010, **49**, 8121–8125. For other applications using the same approach see (b) S. Fleischer, S. Zhou, S. Wermeister, K. Junge, M. Beller, *Chem. Eur. J.,* 2013, **19**, 4997; (c) S. Zhou, S. Fleischer, H. Jao, K. Junge, M. Beller, *Adv. Synth. Catal,* 2014, **356**, 3451.
6 Review: A. Quintard, J. Rodriguez, *Angew. Chem. Int. Ed.,* 2014, **53**, 4044-4055.
7 W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science*, 2013, **342**, 1080-1083.
8 (a) T. T. Thai, D. S. Merel, A. Poater, S. Gaillard, J.-L. Renaud, *Chem. Eur. J.*, 2015, **21**, 7066-7070; (b) for another recent contribution about the use of achiral complexes see: D. S. Merel, S. Gaillard, T. R. Ward, J.-L. Renaud, *Catal. Lett*., 2016, **146**, 564.
9 (a) H.-J. Knölker, J. Heber, C. H. Mahler, *Synlett*, 1992, 1002-1004; (b) H.-J. Knölker, E.Baum, R. Klauss, *Tetrahedron Lett.*, 1995, **36**, 7647-7650.
10 *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, 2010.
11 H.-J. Knölker, E. Baum, H. Goesmann, R. Klauss, *Angew. Chem. Int. Ed.*, 1999, **38**, 2064 – 2068.
12 S. Moulin, H. Dentel, A. Pagnoux-Ozherelyeva, S. Gaillard, P. Sylvain; A. Poater, L. Cavallo, J. F. Lohier, J. L. Renaud, *Chem. Eur. J.*, 2013, **19**, 17881 – 17890.
13 T. Yan, B. L. Feringa, K. Barta, *ACS Catal.*, 2016, **6**, 381-388.
14 Astellas Pharma Inc., Patent: US2014/88080 A1, 2014.
15 Reviews on chiral amines importance in pharmaceutical industry: (a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713–1760; (b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557–2590.
16 (a) M. S. Sudhir, R. V. Nadh, *Drug Invent. Today*, 2013, **5**, 133–138; (b) M. Fernández, E. Barcia, A. Fernández-Carballido, L. Garcia, K. Slowing, S. Negro, *Int. J. Pharm*., 2012, 266–278.
17 (a) M. R. Farlow, J. L. Cummings, *Am. J. Med.,* 2007, **120**, 388–397. (b) For different strategies in the synthesis of Rivastigmine see: P. C. Yan, G. L. Zhu, J. H. Xie, X. D. Zhang, Q. L. Zhou, Y. Q. Li, W. Q. Shen, D. Q. Che, *Org. Process Res. Dev*., 2013, **17**, 307−312. (c) See also D. Brenna, M. Benaglia, R. Porta, S. D. Fernandes, A. J. Burke, *Eur. J. Org. Chem*, 2016, doi:10.1002/ejoc.201601268.
18 D. Brenna, M. Pirola, L. Raimondi, A. J. Burke, M. Benaglia, *Bioorg. Med. Chem.,* 2017**,** *DOI:* 10.1016/j.bmc.2017.01.023 and references cited.
19 A. Von der Höh, A. Berkessel, *ChemCatChem,* 2011, **3**, 861-867.

